The Secrets of Autism  
**The number of children diagnosed with autism and Asperger's in the U.S. is exploding. Why?**   
By [J. Madeleine Nash](mailto:daily@timeinc.net)

Tommy Barrett is a dreamy-eyed fifth-grader who lives with his parents, twin brothers, two cats and a turtle in San Jose, Calif., the heart of Silicon Valley. He's an honor-roll student who likes math and science and video games. He's also a world-class expert on Animorph and Transformer toys. "They're like cars and trains and animals that transform into robots or humans — I love them!" he shouts exuberantly.

And that is sometimes a problem. For a time, in fact, Tommy's fascination with his toys was so strong that when they weren't around he would pretend to be the toys, transforming from a truck into a robot or morphing into a kitten. He would do this in the mall, in the school playground and even in the classroom. His teachers found this repetitive pantomime delightful but disturbing, as did his mother Pam. By that point, there were other worrisome signs. Pam Barrett recalls that as a 3-year-old, Tommy was a fluent, even voluble talker, yet he could not seem to grasp that conversation had reciprocal rules, and, curiously, he avoided looking into other people's eyes. And although Tommy was obviously smart — he had learned to read by the time he was 4 — he was so fidgety and unfocused that he was unable to participate in his kindergarten reading group.

When Tommy turned 8, his parents finally learned what was wrong. Their bright little boy, a psychiatrist informed them, had a mild form of autism known as Asperger syndrome. Despite the fact that children with Asperger's often respond well to therapy, the Barretts, at that moment, found the news almost unbearable.

That's because just two years earlier Pam and her husband Chris, operations manager of a software-design company, had learned that Tommy's twin brothers Jason and Danny were profoundly autistic. Seemingly normal at birth, the twins learned to say a few words before they spiraled into their secret world, quickly losing the abilities they had just started to gain. Instead of playing with toys, they broke them; instead of speaking, they emitted an eerie, high-pitched keening.

First Jason and Danny, now Tommy. Pam and Chris started to wonder about their children's possible exposure to toxic substances. They started scanning a lengthening roster of relatives, wondering how long autism had shadowed their family.

The anguish endured by Pam and Chris Barrett is all too familiar to tens of thousands of families across North America and other parts of the world. With a seeming suddenness, cases of autism and closely related disorders like Asperger's are exploding in number, and no one has a good explanation for it. While many experts believe the increase is a by-product of a recent broadening of diagnostic criteria, others are convinced that the surge is at least in part real and thereby cause for grave concern.

In the Barretts' home state of California, for instance, the number of autistic children seeking social services has more than quadrupled in the past 15 years, from fewer than 4,000 in 1987 to nearly 18,000 today. So common are cases of Asperger's in Silicon Valley, in fact, that Wired magazine coined a cyber-age term for the disorder, referring to its striking combination of intellectual ability and social cluelessness as the "geek syndrome." Wired went on to make a provocative if anecdotal case that autism and Asperger's were rising in Silicon Valley at a particularly alarming rate — and asked [whether "math-and-tech genes" might be to blame.](http://www.time.com/time/covers/1101020506/scaspergers.html)

Yet the rise in autism and Asperger's is hardly confined to high-tech enclaves or to the children of computer programmers and software engineers. It occurs in every job category and socioeconomic class and in every state. "We're getting calls from school systems in rural Georgia," observes Sheila Wagner, director of the Autism Resource Center at Atlanta's Emory University. "People are saying, 'We never had any kids with autism before, and now we have 10! What's going on?'"

It's a good question. Not long ago, autism was assumed to be comparatively rare, affecting as few as 1 in 10,000 people. The latest studies, however, suggest that as many as 1 in 150 kids age 10 and younger may be affected by autism or a related disorder — a total of nearly 300,000 children in the U.S. alone. If you include adults, according to the Autism Society of America, more than a million people in the U.S. suffer from one of the autistic disorders (also known as pervasive developmental disorders or pdds). The problem is five times as common as Down syndrome and three times as common as juvenile diabetes.

No wonder parents are besieging the offices of psychologists and psychiatrists in their search for remedies. No wonder school systems are adding special aides to help teachers cope. And no wonder public and private research institutions have launched collaborative initiatives aimed at deciphering the complex biology that produces such a dazzling range of disability.

In their urgent quest for answers, parents like the Barretts are provoking what promises to be a scientific revolution. In response to the concerns they are raising, money is finally flowing into autism research, a field that five years ago appeared to be stuck in the stagnant backwaters of neuroscience. Today dozens of scientists are racing to identify the genes linked to autism. Just last month, in a series of articles published by Molecular Psychiatry, scientists from the U.S., Britain, Italy and France reported that they are beginning to make significant progress.

Meanwhile, research teams are scrambling to create animal models for autism in the form of mutant mice. They are beginning to examine environmental factors that might contribute to the development of autism and using advanced brain-imaging technology to probe the deep interior of autistic minds. In the process, scientists are gaining rich new insights into this baffling spectrum of disorders and are beginning to float intriguing new hypotheses about why people affected by it develop minds that are strangely different from our own and yet, in some important respects, hauntingly similar.

**AUTISM'S GENETIC ROOTS**   
Autism was first described in 1943 by Johns Hopkins psychiatrist Leo Kanner, and again in 1944 by Austrian pediatrician Hans Asperger. Kanner applied the term to children who were socially withdrawn and preoccupied with routine, who struggled to acquire spoken language yet often possessed intellectual gifts that ruled out a diagnosis of mental retardation. Asperger applied the term to children who were socially maladroit, developed bizarre obsessions and yet were highly verbal and seemingly quite bright. There was a striking tendency, Asperger noted, for the disorder to run in families, sometimes passing directly from father to son. Clues that genes might be central to autism appeared in Kanner's work as well.

But then autism research took a badly wrong turn. Asperger's keen insights languished in Europe's postwar turmoil, and Kanner's were overrun by the Freudian juggernaut. Children were not born autistic, experts insisted, but became that way because their parents, especially mothers, were cold and unnurturing.

In 1981, however, British psychiatrist Dr. Lorna Wing published an influential paper that revived interest in Asperger's work. The disorder Asperger identified, Wing observed, appeared in many ways to be a variant of Kanner's autism, so that the commonalities seemed as important as the differences. As a result, researchers now believe that Asperger and Kanner were describing two faces of a highly complicated and variable disorder, one that has its source in the kaleidoscope of traits encoded in the human genome. Researchers also recognize that severe autism is not always accompanied by compensatory intellectual gifts and is, in fact, far likelier to be characterized by heartbreaking deficits and mental retardation.

Perhaps the most provocative finding scientists have made to date is that the components of autism, far more than autism itself, tend to run in families. Thus even though profoundly autistic people rarely have children, researchers often find that a close relative is affected by some aspect of the disorder. A sister may engage in odd repetitive behavior or be excessively shy; a brother may have difficulties with language or be socially inept to a noticeable degree. In similar fashion, if one identical twin has autism, there is a 60% chance that the other will too and a better than 75% chance that the twin without autism will exhibit one or more autistic traits.

How many genes contribute to susceptibility to autism? Present estimates run from as few as three to more than 20. Coming under intensifying scrutiny, as the papers published by Molecular Psychiatry indicate, are genes that regulate the action of three powerful neurotransmitters: glutamate, which is intimately involved in learning and memory, and serotonin and gamma-aminobutiric acid (gaba), which have been implicated in obsessive-compulsive behavior, anxiety and depression.

Those genes hardly exhaust the list of possibilities. Among the suspects are virtually all the genes that control brain development and perhaps cholesterol and immune-system function as well. Christopher Stodgell, a developmental toxicologist at New York's University of Rochester, observes that the process that sets up the brain resembles an amazingly intricate musical score, and there are tens of thousands of genes in the orchestra. If these genes do what they're supposed to do, says Stodgell, "then you have a Mozart's Concerto for Clarinet. If not, you have cacophony."

**A DIFFERENCE OF MIND**   
Autistic people often suffer from a bewildering array of problems — sensory disturbances, food allergies, gastrointestinal problems, depression, obsessive compulsiveness, subclinical epilepsy, attention-deficit hyperactivity disorder. But there is, researchers believe, a central defect, and that is the difficulty people across the autistic spectrum have in developing a theory of mind. That's psychologese for the realization, which most children come to by the age of 4, that other people have thoughts, wishes and desires that are not mirror images of their own. As University of Washington child psychologist Andrew Meltzoff sees it, the developmental stage known as the terrible twos occurs because children — normal children, anyway — make the hypothesis that their parents have independent minds and then, like proper scientists, set out to test it.

Children on the autistic spectrum, however, are "mind blind"; they appear to think that what is in their mind is identical to what is in everyone else's mind and that how they feel is how everyone else feels. The notion that other people — parents, playmates, teachers — may take a different view of things, that they may harbor concealed motives or duplicitous thoughts, does not readily occur. "It took the longest time for Tommy to tell a lie," recalls Pam Barrett, and when he finally did, she inwardly cheered.

Meltzoff believes that this lack can be traced to the problem that autistic children have in imitating the adults in their lives. If an adult sits down with a normal 18-month-old and engages in some interesting behavior — pounding a pair of blocks on the floor, perhaps, or making faces — the child usually responds by doing the same. Young children with autism, however, do not, as Meltzoff and his colleague Geraldine Dawson have shown in a series of playroom experiments.

The consequences of this failure can be serious. In the early years of life, imitation is one of a child's most powerful tools for learning. It is through imitation that children learn to mouth their first words and master the rich nonverbal language of body posture and facial expression. In this way, Meltzoff says, children learn that drooping shoulders equal sadness or physical exhaustion and that twinkling eyes mean happiness or perhaps mischievousness.

For autistic people — even high-functioning autistic people — the ability to read the internal state of another person comes only after long struggle, and even then most of them fail to detect the subtle signals that normal individuals unconsciously broadcast. ["I had no idea that other people communicated through subtle eye movements," says autistic engineer Temple Grandin,](http://www.time.com/time/covers/1101020506/scmyself.html) "until I read it in a magazine five years ago."

At the same time, it is incorrect to say autistic people are cold and indifferent to those around them or, as conventional wisdom once had it, lack the high-level trait known as empathy. Last December, when Pam Barrett felt overwhelmed and dissolved into tears, it was Danny, the most deeply autistic of her children, who rushed to her side and rocked her back and forth in his arms.

Another misperception about people with autism, says Karen Pierce, a neuroscientist at the University of California at San Diego, is the notion that they do not register faces of loved ones as special — that, in the words of a prominent brain expert, they view their own mother's face as the equivalent of a paper cup. Quite the contrary, says Pierce, who has results from a neuroimaging study to back up her contention. Moreover, the center of activity in the autistic mind, she reported at a conference held in San Diego last November, turns out to be the fusiform gyrus, an area of the brain that in normal people specializes in the recognition of human faces.

In a neuroimaging study, Pierce observed, the fusiform gyrus in autistic people did not react when they were presented with photographs of strangers, but when photographs of parents were substituted, the area lit up like an explosion of Roman candles. Furthermore, this burst of activity was not confined to the fusiform gyrus but, as in normal subjects, extended into areas of the brain that respond to emotionally loaded events. To Pierce, this suggests that as babies, autistic people are able to form strong emotional attachments, so their social aloofness later on appears to be the consequence of a brain disorganization that worsens as development continues.

In so many ways, study after study has found, autistic people do not parse information as others do. University of Illinois psychologist John Sweeney, for example, has found that activity in the prefrontal and parietal cortex is far below normal in autistic adults asked to perform a simple task involving spatial memory. These areas of the brain, he notes, are essential to planning and problem solving, and among their jobs is keeping a dynamically changing spatial map in a cache of working memory. As Sweeney sees it, the poor performance of his autistic subjects of the task he set for them — keeping tabs on the location of a blinking light — suggests that they may have trouble updating that cache or accessing it in real time.

To Sweeney's collaborator, University of Pittsburgh neurologist Dr. Nancy Minshew, the images Sweeney has produced of autistic minds in action are endlessly evocative. They suggest that essential connections between key areas of the brain either were never made or do not function at an optimal level. "When you look at these images, you can see what's not there," she says, conjuring up an experience eerily akin to looking at side-by-side photographs of Manhattan with and without the Twin Towers.

**A MATTER OF MISCONNECTIONS**   
Does autism start as a glitch in one area of the brain — the brainstem, perhaps — and then radiate out to affect others? Or is it a widespread problem that becomes more pronounced as the brain is called upon to set up and utilize increasingly complex circuitry? Either scenario is plausible, and experts disagree as to which is more probable. But one thing is clear: very early on, children with autism have brains that are anatomically different on both microscopic and macroscopic scales.

For example, Dr. Margaret Bauman, a pediatric neurologist at Harvard Medical School, has examined postmortem tissue from the brains of nearly 30 autistic individuals who died between the ages of 5 and 74. Among other things, she has found striking abnormalities in the limbic system, an area that includes the amygdala (the brain's primitive emotional center) and the hippocampus (a seahorse-shaped structure critical to memory). The cells in the limbic system of autistic individuals, Bauman's work shows, are atypically small and tightly packed together, compared with the cells in the limbic system of their normal counterparts. They look unusually immature, comments University of Chicago psychiatrist Dr. Edwin Cook, "as if waiting for a signal to grow up."

An intriguing abnormality has also been found in the cerebellum of both autistic children and adults. An important class of cells known as Purkinje cells (after the Czech physiologist who discovered them) is far smaller in number. And this, believes neuroscientist Eric Courchesne, of the University of California at San Diego, offers a critical clue to what goes so badly awry in autism. The cerebellum, he notes, is one of the brain's busiest computational centers, and the Purkinje cells are critical elements in its data-integration system. Without these cells, the cerebellum is unable to do its job, which is to receive torrents of information about the outside world, compute their meaning and prepare other areas of the brain to respond appropriately.

Several months ago, Courchesne unveiled results from a brain-imaging study that led him to propose a provocative new hypothesis. At birth, he notes, the brain of an autistic child is normal in size. But by the time these children reach 2 to 3 years of age, their brains are much larger than normal. This abnormal growth is not uniformly distributed. Using mri-imaging technology, Courchesne and his colleagues were able to identify two types of tissue where this mushrooming in size is most pronounced.

These are the neuron-packed gray matter of the cerebral cortex and white matter, which contains the fibrous connections projecting to and from the cerebral cortex and other areas of the brain, including the cerebellum. Perhaps, Courchesne speculates, it is the signal overload caused by this proliferation of connections that injures the Purkinje cells and ultimately kills them. "So now," says Courchesne, "a very interesting question is, What's driving this abnormal brain growth? If we could understand that, then we might be able to slow or stop it."

A proliferation of connections between billions of neurons occurs in all children, of course. A child's brain, unlike a computer, does not come into the world with its circuitry hard-wired. It must set up its circuits in response to a sequence of experiences and then solder them together through repeated neurological activity. So if Courchesne is right, what leads to autism may be an otherwise normal process that switches on too early or too strongly and shuts off too late — and that process would be controlled by genes.

Currently Courchesne and his colleagues are looking very closely at specific genes that might be involved. Of particular interest are the genes encoding four brain-growth regulators that have been found in newborns who go on to develop mental retardation or autism. Among these compounds, as National Institutes of Health researcher Dr. Karin Nelson and her colleagues reported last year, is a potent molecule known as vasoactive intestinal peptide. vip plays a role not only in brain development but in the immune system and gastrointestinal tract as well, a hint that other disorders that so frequently accompany autism may not be coincidental.

The idea that there might be early biomarkers for autism has intrigued many researchers, and the reason is simple. If one could identify infants at high risk, then it might become possible to monitor the neurological changes that presage the onset of behavioral symptoms, and someday perhaps even intervene in the process. "Right now," notes Michael Merzenich, a neuroscientist at the University of California, San Francisco, "we study autism after the catastrophe occurs, and then we see this bewildering array of things that these kids can't do. What we need to know is how it all happened."

The genes that set the stage for autistic disorders could derail developing brains in a number of ways. They could encode harmful mutations like those responsible for single-gene disorders — cystic fibrosis, for instance, or Huntington's disease. They could equally well be garden-variety variants of normal genes that cause problems only when they combine with certain other genes. Or they could be genes that set up vulnerabilities to any number of stresses encountered by a child.

A popular but still unsubstantiated theory [blames autism on the MMR (measles, mumps and rubella) vaccine, which is typically given to children at around 15 months](http://www.time.com/time/covers/1101020506/scvaccine.html). But there are many other conceivable culprits. Researchers at the University of California at Davis have just launched a major epidemiological study that will test the tissues of both autistic and nonautistic children for residues of not only mercury but also pcbs, benzene and other heavy metals. The premise is that some children may be genetically more susceptible than others to damage by these agents, and so the study will also measure a number of other genetic variables, like how well these children metabolize cholesterol and other lipids.

Drugs taken by some pregnant women are also coming under scrutiny. At the University of Rochester, embryologist Patricia Rodier and her colleagues are exploring how certain teratogens (substances that cause birth defects) could lead to autism. They are focusing on the teratogens' impact on a gene called hoxa1, which is supposed to flick on very briefly in the first trimester of pregnancy and remain silent ever after. Embryonic mice in which the rodent equivalent of this gene has been knocked out go on to develop brainstems that are missing an entire layer of cells.

In the end, it is not merely possible but likely that scientists will discover multiple routes — some rare, some common; some purely genetic, some not — that lead to similar end points. And when they do, new ideas for how to prevent or correct autism may quickly materialize. A decade from now, there will almost certainly be more effective forms of therapeutic intervention, perhaps even antiautism drugs. "Genes," as the University of Chicago's Cook observes, "give you targets, and we're pretty good at designing drugs if we know the targets."

Paradoxically, the very thing that is so terrible about autistic disorders — that they affect the very young — also suggests reason for hope. Since the neural connections of a child's brain are established through experience, well-targeted mental exercises have the potential to make a difference. One of the big unanswered questions, in fact, is why 25% of children with seemingly full-blown autism benefit enormously from intensive speech- and social-skills therapy — and why the other 75% do not. Is it because the brains of the latter are irreversibly damaged, wonders Geraldine Dawson, director of the University of Washington's autism center, or is it because the fundamental problem is not being adequately addressed?

The more scientists ponder such questions, the more it seems they are holding pieces of a puzzle that resemble the interlocking segments of Tommy Barrett's Transformer toys. Put the pieces together one way, and you end up with a normal child. Put them together another way, and you end up with a child with autism. And as one watches Tommy's fingers rhythmically turning a train into a robot, a robot into a train, an unbidden thought occurs. Could it be that some dexterous sleight of hand could coax even profoundly autistic brains back on track? Could it be that some kid who's mesmerized by the process of transformation will mature into a scientist who figures out the trick?